Some Formylation Reactions of Imidazo[1,5-*a*]pyridine and Pyrrocoline

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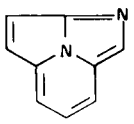
As part of our studies directed towards the synthesis of 2-azacycl[3,2,2]azine (**1**) (1), we had occasion to formylate 5-methylimidazo[1,5-*a*]pyridine (**2**) and now wish to report the results of these formylation studies on compound **2**, imidazo[1,5-*a*]pyridine (**3**), and pyrrocoline (**4**).



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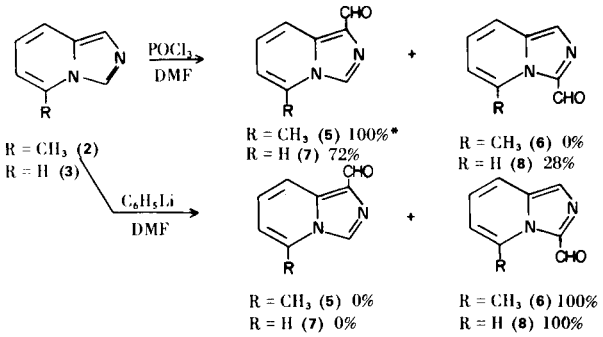
When 5-methylimidazo[1,5-*a*]pyridine (**2**) was treated with phosphorus oxychloride in dimethylformamide a mono-formyl derivative (**5**) was obtained which was isomeric with the monoformyl derivative (**6**) obtained by treatment of compound **2** with phenyl lithium in dimethylformamide.

An examination of the pmr spectra of compounds **5** and **6** (see Table I), clearly shows that the formyl group in these compounds must be in the five-membered ring. Thus, one of the formyl derivatives is a 1-substituted imidazo[1,5-*a*]pyridine derivative, while the other is a 3-substituted one.

A close examination of the chemical shifts of the 6-membered ring protons and a comparison with the chemical shifts of the same protons in 5-methylimidazo[1,5-*a*]-pyridine (**2**) shows that H-8 in the formyl compound derived *via* the phosphorus oxychloride-dimethyl formamide reaction, is considerably more deshielded than the same proton in the formyl derivative obtained *via* the phenyl lithium-dimethyl formamide reaction. Thus, we can conclude that the phorphorus oxychloride-dimethylformamide reaction affords the 1-formyl (**5**) and the butyllithium-dimethylformamide the 3-formyl (**6**) derivative.

Similar results (see Table II) were obtained with imidazo[1,5-*a*]pyridine (**3**) itself, except that the phosphorus oxychloride-dimethylformamide reaction affords a trace of the 3-formyl derivative (**8**) along with the major component, the 1-formyl derivative (**7**). These reactions are delineated in Scheme I.

Scheme I



*The percentages given are relative values.

In view of the great selectivity exhibited by the two different formylation reactions, it now became of interest to examine the behavior of pyrrocoline (**4**) towards these reagents. (Scheme II).

Amazingly, the reaction of pyrrocoline (**4**) with phosphorus oxychloride-dimethylformamide affords two monoformyl derivatives. An examination of the pmr spectra (see Table I) and an analysis similar to the one delineated for the 5-methylimidazo[1,5-*a*]pyridine instance allows us to assign the 3-formyl structure (**9**) to the major product, and the 1-formyl structure (**10**) to the minor one.

This difference in behavior between imidazo[1,5-*a*]-pyridine (**3**) and pyrrocoline (**4**), prompted us to attempt a typical electrophilic substitution reaction on pyrrocoline.

Scheme II

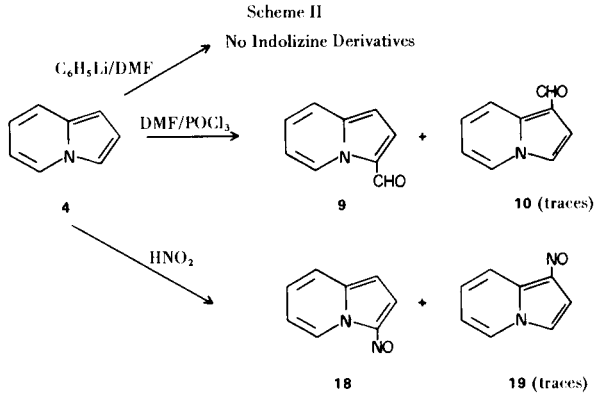
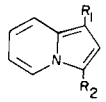
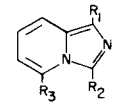


Table I

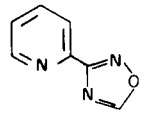
Pmr Spectral Data of some Indolizines and Imidazo[1,5-*a*]pyridines

Compound (#)	Chemical Shifts (τ)								Coupling Constants (hz)				
	H_1	H_9	H_3	H_5	H_6	H_7	H_8	SUBST.	J_{12}	J_{23}	J_{56}	J_{67}	J_{78}
													
$R_1 = R_2 = H$ (**4**)	3.72	3.36	2.86	2.24	3.69	3.50	2.75		3.90	2.74	6.82	6.39	8.98
$R_1 = H, R_2 = CH$ (**9**) 	3.59	2.73	----	0.48	3.30	2.99	2.61	0.41	5.00	----	7.00	7.00	9.00
$R_1 = CHO, R_2 = H$ (**10**)	----	2.73	2.86	2.08	3.30	2.99	1.92	0.12	----	2.90	7.00	7.00	9.00
$R_1 = NO, R_2 = H$ (**19**)	----	2.50	3.35	2.83	2.92	2.50	0.40	---	---	3.00	7.00	7.00	9.00
$R_1 = H, R_2 = NO$ (**18**)	3.23	1.96	----	-0.16	2.90	2.43	2.43	---	5.00	----	7.00	7.00	~9.00 (a)
													
$R_1 = R_2 = R_3 = H$ (**3**)	2.73	----	2.03	2.12	3.59	3.42	2.66	---	----	----	7.13	6.38	9.21
$R_1 = R_3 = H, R_2 = CHO$ (**8**)	2.28	----	----	0.54	3.00	2.88	2.30	0.03	----	----	7.00	7.00	9.00
$R_1 = CHO; R_2 = R_3 = H$ (**7**)	----	----	1.85	1.74	3.12	2.80	1.92	-0.04	----	----	7.00 (a)	7.00	9.00
$R_1 = R_2 = H; R_3 = CH_3$ (**2**)	2.59	----	2.10	----	3.88	3.51	2.81	7.70	----	----	----	7.00	9.00
$R_1 = H, R_2 = CHO, R_3 = CH_3$ (**6**)	2.27	----	----	----	3.25	2.89	2.50	7.12 (CH_3); 0.07 (CHO)	----	----	----	7.00	9.00
$R_1 = CHO, R_2 = H, R_3 = CH_3$ (**5**)	----	----	1.97	----	3.33	2.86	1.88	7.0 (CH_3); -0.08 (CHO)	---	---	----	7.00	9.00

(a) Estimated value because of peak overlaps.

The reaction studied, nitrosation, afforded *two* isomeric nitroso compounds whose pmr spectra (see Table I) allow us to assign the 1- and 3-nitroso structures respectively, to them.

Again, this behavior is significantly different from that of imidazo[1,5-*a*]pyridine under identical conditions (11), where the rearrangement product **11**, is obtained.



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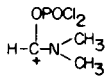
Indolizines have been reported to afford 3-acetyl derivatives upon acetylation when the 1-position is occupied or 1-acetyl derivatives when the 3 position is substituted (7). A similar pattern of substitution has been observed on some 2-substituted indolizines upon nitrosation (8).

There now remains to discuss some possible mechanisms to account for the formation of the various products. It has been well established that the dimethylformamide-phosphorus oxychloride type formylation reactions (Vills-meier formylation) occurs *via* an electrophilic substitution reaction involving a species such as **12**.



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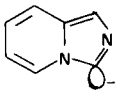
And that the phenyllithium-dimethylformamide reaction involves the prior generation of an anion intermediate, exemplified by structure **13**.



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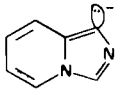
Thus, the formation of 1-formyl imidazo[1,5-*a*]pyridines by attack of the electrophilic agent **12** at position 1 is not surprising. Similarly, in view of the base-catalyzed H → D exchange studies on imidazo[1,5-*a*]pyridine (9), the preferential generation of the anion **13**, over its alternative



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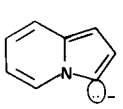
14, is acceptable, and accounts for the formation of the 3-formyl derivatives as the major products in this ring system.

An examination of the indolizine ring system leads to the following interesting conclusion: Anion **15** would be expected to be more stable than anion **16** in view of the



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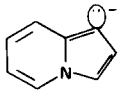

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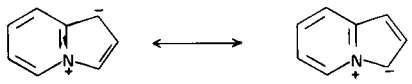
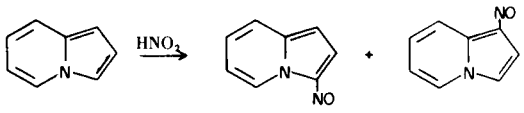
stabilizing influence that the somewhat positive (**17**) bridge-nitrogen atom would have upon it. However, it appears that in the absence of an additional nitrogen atom in the five-membered ring, these anions are not stable. The preferential formylation at position 3, under electrophilic substitution conditions, might be accounted for by possible complexing of the highly electronetative phosphorus end of **12** with the bridge-nitrogen atom involving the resonance contributor, **17b**.



a *b*

17

There now remains a need to comment on the fact that nitrosation affords both a 3-nitroso- (**18**) as well as 1-nitroso derivative (**19**).



4 18 19

It is clear that the possibility of the ^{+}NO complexing with the pyrrocoline nitrogen is much less than is the case with species **12**, thus, both of the resonance contributors (**17a** and **17b**) will be involved (10).

EXPERIMENTAL

1-Formylimidazo[1,5-*a*]pyridine (7).

To an ice-water cooled solution of imidazo[1,5-*a*]pyridine (2) (0.59 g., 5 mmoles) in dry DMF (0.40 g., 5.5 mmoles) was added with stirring and dropwise, freshly distilled phosphorus oxychloride (1.07 g., 7 mmoles). After one hour of heating on a steam bath, the reaction mixture was cooled and poured into ice-water. The resulting solution was made basic with concentrated ammonium hydroxide and extracted with chloroform. The combined extracts (3 x 200 ml.) were dried over anhydrous sodium carbonate and evaporated to dryness. The resulting brown solid (3) was placed into a soxhlet extractor and extracted with ethyl ether. Further purification of the solid by sublimation afforded 0.203 g. (28.2%) of a yellow solid, m.p. = 124-125°, pmr (see Table I); mass spectrum: (70 e/v) m/e 146 (M^+), 145 (M^+-1), 117 (M^+-29), 90 (M^+-56).

Anal. Calcd. for $C_8H_6N_2O$: C, 65.80; H, 4.10; N, 19.20. Found: C, 65.86; H, 4.14; N, 19.13.

1-Formaldoximoimidazo[1,5-*a*]pyridine.

To 1-formylimidazo[1,5-*a*]pyridine (0.056 g., 0.35 mmole) in 10 ml. of methanol-water was added 5 ml. of an aqueous solution of 0.03 g. (0.43 mmole) of hydroxylamine hydrochloride. The

solution was made basic with solid potassium carbonate and heated gently. Upon cooling, a burnt-yellow solid separated. Separation of the solid by filtration and recrystallization from methanol-water gave 35 mg. (57.2%) of pure formaldoxime, m.p. = 162-163°; pmr (DMSO, δ (ppm)): 8.50-8.36 (m, 2H), 8.26 (s, 1H), 8.26 (s, 2H), 7.82 (d, 1H, J = 10 Hz), 7.07-6.65 (m, 2H); mass spectrum: (70 ev) m/e 161 (M^+), 143 (M^+-18), 131 (M^+-30), Ir (KBr) 3490 (OH), 1675 (-C=N-) cm^{-1}.

Anal. Calcd. for $C_8H_7N_3O$: C, 59.60; H, 4.35; N, 26.10. Found: C, 59.66; H, 4.45; N, 26.13.

3-Formylimidazo[1,5-*a*]pyridine (**8**).

To an ice-cooled solution of imidazo[1,5-*a*]pyridine (2.0 g., 0.0169 mole) in 30 ml. of anhydrous ethyl ether was added with stirring 10 ml. of 2*M* phenyllithium solution (in hexane) under a nitrogen atmosphere. The reddish solution was stirred for three hours and then dry DMF (2 g., 0.0274 mole) was added dropwise. The reaction mixture was allowed to warm up slowly to room temperature. Water was then added to quench the reaction and the reaction mixture was acidified with dilute hydrochloric acid and washed with ethyl ether. The aqueous layer was separated, made basic with sodium carbonate and extracted with chloroform. The chloroform layer was dried over anhydrous sodium carbonate and evaporated to dryness. The resulting brown solid was purified by sublimation to give 325 mg. of the 3-formylimidazo[1,5-*a*]-pyridine (13.2%), m.p. = 61-62°, pmr (see Table I); mass spectrum: (70 ev) m/e 146 (M^+), 145 (M^+-1), 117 (M^+-29).

Anal. Calcd. for $C_8H_6N_2O$: C, 65.80; H, 4.10; N, 19.20. Found: C, 66.09; H, 4.19; N, 19.25.

3-Formaldoximoimidazo[1,5-*a*]pyridine.

To 3-formylimidazo[1,5-*a*]pyridine (75 mg., 0.472 mmole) in 15 ml. of methanol-water was added a solution of hydroxylamine hydrochloride (38 mg., 0.546 mmole) in 7 ml. of water. The mixture was gently heated and made basic with solid potassium carbonate to yield a white solid. After 15 minutes of heating the solution was cooled and the solid was collected by filtration. Recrystallization from methanol-water gave imidazo[1,5-*a*]pyridine, 3-formaldoxime, 50 mg. (61%), m.p. = 62-63°; pmr (DMSO, TMS): δ = 9.26 (d, 1H, J = 8 Hz) δ = 8.74 (s, 1H), δ = 8.14-7.90 (m, 1H), δ = 7.94 (s, 1H), δ = 7.40-7.16 (m, 2H); mass spectrum: (70 ev) m/e 161 (M^+), 143 (M^+-18), 131 (M^+-30) 117 (M^+-44).

Anal. Calcd. for $C_8H_7N_3O$: C, 59.60; H, 4.35; N, 26.10. Found: C, 59.54; H, 4.38; N, 26.16.

1-Formyl-5-methylimidazo[1,5-*a*]pyridine (**5**).

To ice-water cooled solution of 5-methylimidazo[1,5-*a*]pyridine (1.22 g., 0.0093 mole) in DMF (0.95 g., 0.013 mole) was added dropwise and with stirring phosphorus oxychloride (1.53 g., 0.013 mole). A strongly exothermic reaction occurred. After 10 minutes of heating on a steam-bath, the mixture was poured into ice-water made basic with concentrated ammonium hydroxide and extracted with chloroform (250 ml.). The chloroform extract was dried over anhydrous sodium carbonate and evaporated to dryness. Purification of the solid by sublimation or extraction with ethyl ether gave a yellow solid (1.0 g., 67.5%), m.p. = 146-147°; pmr (see Table I); mass spectrum: (70 ev) m/e 160 (M^+), 159 (M^+-1), 131 (M^+-29), 104 (M^+-56).

Anal. Calcd. for $C_9H_8N_2O$: C, 67.50; H, 5.00; N, 17.50. Found: C, 67.60; H, 5.02; N, 17.54.

3-Formyl-5-methylimidazo[1,5-*a*]pyridine (**6**).

To a stirred solution of 5-methylimidazo[1,5-*a*]pyridine (12.2 g., 0.093 mole) in 50 ml. of anhydrous ether, at 0°, was added 50 ml. of 2*M* phenyllithium solution (in hexane) by means of a syringe and under a nitrogen atmosphere. After three hours of stirring, dry DMF (7.3 g., 0.1 mole) was added dropwise while the mixture was still at 0°. The mixture was then refluxed for 15 minutes at room temperature and water was added to the solution followed by acidification with dilute hydrochloric acid. The crude product was washed with ether and the aqueous layer was separated and made basic with sodium carbonate. The basic solution was extracted with chloroform, dried over anhydrous sodium carbonate and the solvent was removed by evaporation. The resulting brown solid was sublimed to give a yellow solid (6.46 g., 43.6%), m.p. 102-103°; pmr (see Table I); mass spectrum: (70 ev) m/e 160 (M^+), 159 (M^+-1), 131 (M^+-29), 104 (M^+-56).

Anal. Calcd. for $C_9H_8N_2O$: C, 67.50; H, 5.00; N, 17.50. Found: C, 67.89; H, 5.07; N, 16.98.

1-Formaldoximo-5-methylimidazo[1,5-*a*]pyridine.

Reaction of 5-methyl-1-formylimidazo[1,5-*a*]pyridine with hydroxylamine hydrochloride and work-up as described before, gave a brown light solid recrystallized from ethanol-water in 59% yield, m.p. 217-218°; mass spectrum: (70 ev) m/e 175 (M^+), 157 (M^+-18), 131 (M^+-44), 103 (M^+-72).

Anal. Calcd. for $C_9H_9N_3O$: C, 61.71; H, 1.75; N, 24.00. Found: C, 61.70; H, 1.77; N, 24.12.

3-Formaldoximo-5-methylimidazo[1,5-*a*]pyridine.

Reaction of 3-formyl-5-methylimidazo[1,5-*a*]pyridine with hydroxylamine hydrochloride and work-up of the mixture as described before gave a burnt-yellow solid which was recrystallized from dimethylsulfoxide-water in 58% yield; m.p. 192-193°; mass spectrum: (70 ev) m/e 175 (M^+), 157 (M^+-18), 129 (M^+-26) 103 (M^+-72).

Anal. Calcd. for $C_9H_9N_3O$: C, 61.71; H, 1.75; N, 24.00. Found: C, 61.80; H, 1.80; N, 23.88.

3-Formylindolizine (**9**).

To a stirred solution of indolizine (4) (2 g., 0.017 mole) in 20 ml. of warm DMF was added dropwise a previously prepared Vills-meier reagent (2.764 g. of phosphorus oxychloride in 6 ml. of DMF). The mixture was stirred for two hours at room temperature. The reaction mixture was then poured into ice (30 g.) and 20 ml. of 25% sodium hydroxide was added. The mixture was refluxed for 15 minutes and filtered. The filtrate was extracted with chloroform (200 ml.), dried over anhydrous sodium carbonate and evaporated to dryness. The excess of DMF was removed by distillation and the dark liquid (5) was vacuum distilled to give a dark-blue liquid (**9**) at 107-108° 1.0 mm Hg (1.12 g., 45.3%); pmr (see Table I); mass spectrum (70 ev) m/e 145 (M^+), 144 (M^+-1), 116 (M^+-29), 89 (M^+-56); ir (neat): 2800, 2780, 1666-1625 cm^{-1} (-C=O).

Anal. Calcd. for C_9H_7NO: C, 72.18; H, 5.26; N, 10.52. Found: C, 72.59; H, 5.19; N, 10.40.

3-Nitrosoindolizine (**18**).

To a stirred solution of indolizine (0.585 g., 5 mmoles) in 15 ml. of 5*N* hydrochloric acid, at 0°, was added dropwise a solution of 2.5 g. of sodium nitrite in 7 ml. of water. After two hours of stirring, the solution was made basic with sodium bicarbonate and extracted with chloroform. The extract was dried over anhydrous sodium carbonate and evaporated to dryness. The resulting solid (6) was very carefully sublimated to give a green solid (0.350 mg., (48%), m.p. 71-72°; pmr (see Table I); mass spectrum: (70 ev) m/e 146 (M^+), 116 (M^+-30), 104 (M^+-42), 89 (M^+-57).

Anal. Calcd. for $C_8H_6N_2O$: C, 65.75; H, 4.10; N, 19.24. Found: C, 65.78; H, 4.34; N, 19.31.

REFERENCES

(1) O. Fuentes and W. W. Paudler, *J. Org. Chem.*, in press (1975).

(2) J. D. Bower and G. L. Ramage, *J. Chem. Soc.*, 2834 (1955).

(3) Pmr analysis of the crude reaction mixture showed the presence of the 1 and 3-formyl derivatives in a ratio of 2.6:1.

(4) V. Boekelheide and J. R. Wingassen, *J. Am. Chem. Soc.*, **81**, 1456 (1959).

(5) Pmr analysis showed the presence of the 1 and 3-formyl derivatives in a ratio of 1.0:4.5.

(6) Pmr analysis showed the presence of the 3- and 1-nitroso derivatives in a tatio of 4.8:1.0.

(7) D. E. Ames, R. F. Grey and W. A. Jones, *J. Chem. Soc.*, 620 (1959), and references therein.

(8) N. P. Buu-Hoi, N. Hoan and R. Royar, *Bull. Soc. Chim. France*, 489 (1950).

(9) W. W. Paudler and L. S. Helmick, *J. Org. Chem.*, **33**, 1087 (1968).

(10) The authors are aware of the dangers involved in using ground-state electron density distribution to reaction intermediates. However, in most heterocyclic systems this argument is acceptable because of rather minor changes involved in formation of the transition states.

(11) W. W. Paudler and J. E. Kuder, *J. Org. Chem.*, **32**, 2430 (1967).